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Workshop report

Identification of subjects with a high risk of developing Type 1 (insulin-dependent) diabetes

Summary of a Workshop held on 25 May 1984 at the Children's Hospital, Basel, Switzerland

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The purpose of this meeting was to review and discuss the currently available immunological and genetic markers of subjects with an increased risk of developing Type 1 (insulin-dependent) diabetes. The conference was sponsored by the Swiss Academy of Medical Sciences and organized by the Division of Diabetology, University Hospital of Basel, Switzerland.

Thirty-five investigators and clinicians from Denmark, FRG, Italy, Sweden, Switzerland and the UK attended the meeting, and the most recent findings on the subject were presented. The topic of the morning session was whether genetic or immunological markers may identify subjects at risk. In the afternoon session, the question of screening certain populations at risk, particularly non-diabetic relatives of Type 1 diabetic subjects, was discussed in order to learn more about the natural history of the 'prediabetic' state, with the ultimate goal of preventing the development of overt disease.

Genetic and immunological markers for Type 1 diabetes in non-diabetic individuals

Two papers reported the prevalence of islet cell antibodies (ICA) in relation to HLA genotypes in first-degree relatives of Type 1 diabetic patients. Dr. K. Spencer (London) observed over a period of 5 years that in 670 first-degree relatives in the 'Bart-Windsor Family Study' 2.6% had complement fixing antibodies (CF-ICA), although their presence was found to fluctuate. HLA-identical siblings had a higher risk of developing ICA (8.8% CF-ICA-positive), but only seven relatives developed Type 1 diabetes over the 5-year period. Six of the seven were CF-ICA-positive, and three were HLA identical, the others being HLA haplo-identical with the proband. These markers were significantly more prevalent in relatives compared with control subjects. However, it was pointed out that diabetes-associated HLA antigens occur frequently in non-diabetic Europeans, i.e. in 50% of healthy subjects, either DR3 or DR4 is observed. These observations on the prevalence of ICA and HLA give these two factors a low specificity for detecting early Type 1 diabetes.

Data from a survey in Basel (Dr. W. Berger) on non-diabetic relatives yielded a similar prevalence of CF-ICA (6%). The point was made in the discussion that both studies were performed on teenage or adult subjects, and a higher yield of diabetic siblings may have been obtained if younger subjects had been screened. However, these studies still demonstrate that a large population sample needs to be analysed in order to detect a significant number of 'prediabetic' subjects.

It was also pointed out by Drs. T. Neri (Parma) and J. Nerup (Gentofte) that new markers, e.g. subtypes of HLA antigens DR3 or DR4 with a higher specificity, may turn out to improve the diagnostic value of these measurements in the future. The role of ICA as a marker for autoimmunity is a controversial issue. It was emphasized by Dr. Nerup that it was not clear at present whether the appearance of ICA reflects autoimmune destruction at the level of the pancreatic B cell, or whether fluctuating ICA represent relapsing insulitis. It was also pointed out by Dr. H. Kolb (Düsseldorf) that the reproducability of ICA measurements from one laboratory to another was poor, particularly at low titres of ICA. The assay problem is not easily resolved, since it is, by definition, semi-quantitative and depends on a variable 'probe', i.e. a slice of human pancreas used for indirect immunofluorescence.

Data were presented on the specificity of ICA by Drs. K. Helmke and K. Federlin (Giessen), demonstrating that viral infections, such as mumps, or even mumps vaccination, can cause the appearance of ICA in children. Four cases of Type 1 diabetes after mumps vaccination were reported. However, these data were retrospective and from a large number of vaccinated children. There is no evidence from prospective studies that either mumps or mumps vaccination can cause diabetes.

A novel abnormality of immune response in relatives of Type 1 diabetic patients was reported by Dr. I. Sklenar (Basel), suggesting that cultivated lymphocytes from such subjects demonstrate decreased proliferation rates when insulin is used as stimulant, and increase suppressor T-cell activity.

A paper by Dr. H. Kolb (Düsseldorf) supported previous observations that ICA determination would be of clinical importance in early identification of B-cell failure in non-insulin-requiring elderly subjects. This assay distinguishes Type 2 (non-insulin-dependent) from Type 1 diabetic patients with late onset and slowly progressive B-cell failure. It was suggested that early insulin treatment in these Type 1 diabetic subjects might preserve B-cell function.

Problems associated with clinical studies for detecting 'prediabetic' subjects in the population using immunological and genetic markers

The difficulties encountered with a multicentre study for detecting 'prediabetic' individuals among relatives of Type 1 diabetic patients were illustrated by Dr. J. Ludvigsson (Umea), who had tried such a study. The following questions remained to be answered before starting work: Who should be studied? Who should be followed? How often should the subjects be examined? What parameters should be analysed? Furthermore, multicentre trials carry the inherent difficulty that the 'disease' of the prediabetic state and the incidence of immunological and genetic markers, may vary from country to country. In addition, environmental (e.g. viral) factors may be different. Due to the lack of standards for measuring ICA, its assay has to be performed in a single laboratory, requiring shipment of plasma samples. Due to the geographical variability of the incidence of Type 1 diabetes (Dr. A. Teuscher, Bern), knowledge of the local incidence is necessary to esti-

mate the risk of developing the disease. A severe ethical problem may also arise in undertaking such a trial. Should the identified risk individuals be told about the potential disease since no treatment can be offered? If they are not told, can non-diabetic youngsters and their parents be motivated to participate in such a trial?

An important question was raised: whether a trial using immunosuppressive therapy (e.g. cyclosporin A, CyA) should be considered to prevent the development of overt disease. This point was discussed after Dr. J. Nerup's presentation of a Canadian trial on the effects of CyA in newly diagnosed Type 1 diabetic patients. This study demonstrated diminished insulin requirements and disappearance of ICA in a significant number of Type 1 diabetic patients of recent onset during CyA treatment. In several cases ICA reappeared after discontinuation of the drug. However, considering the side-effects of the drug and the poor specificity of the immunogenetic markers, only a carefully planned, prospective, multicentre trial of the effects of CyA on residual B-cell function, ICA and clinical outcome would be justified. Results of such trials should be awaited before CyA or other immunosuppressant agents are used in patients or their relatives.

After a final discussion, it was concluded that the occurrence of ICA represents an increased risk of developing overt Type 1 diabetes in non-diabetic siblings of Type 1 diabetic patients, and of developing insulin dependence in subjects thought to have non-insulin-dependent diabetes.

Future trials should clarify the following questions in populations of sufficient size:

1. What environmental (e.g. viral) or genetic factors mediate the appearance or disappearance of ICA in non-diabetic subjects?
2. What other humoral or cell-mediated abnormalities are present in ICA-positive 'prediabetic' subjects?
3. Are there immunological or genetic markers which provide a more specific parameter of B-cell destruction and the final development of overt disease compared with ICA?
4. What is the relationship between the appearance of ICA and B-cell function?

Answers to these questions are necessary to improve our knowledge of the 'prediabetic' state. Further data on this issue should not only shed light on the pathogenesis of Type 1 diabetes, but should also open new roads for therapeutic intervention.

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